Evaluation and Treatment of TB Contacts
Tyler, Texas
April 11, 2014

Diagnosis and Medical Management of TB Disease
David Griffith, BA, MD
April 11, 2014

David Griffith, BA, MD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Diagnosis and Medical Management of Tuberculosis

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Professor of Medicine
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Heartland National TB Center

Diagnosis of Tuberculosis

• Clinical suspicion is the single most important factor in the timely diagnosis of tuberculosis.
• The greatest risk for nosocomial transmission of tuberculosis is exposure to an undiagnosed case of TB.
• There is no diagnostic substitute for thinking about the diagnosis.
• Clinical judgment is second only to clinical suspicion in importance (know when to pull the trigger)
Reasons a Diagnosis of TB is Missed or Delayed

- Patient is diagnosed as a community acquired pneumonia and responds to a fluoroquinolone (more than one course required for FQ resistance)
- Atypical clinical and radiographic picture
- Extrapulmonary disease
- Clinician does not consider TB as a diagnostic possibility (PCP, ED, specialist, radiologist)
Standard Components of TB/LTBI Evaluation

- If TST or IGRA Positive
  - Patient History
  - Physical examination
  - Radiologic evaluation
  - ?Laboratory?

Patient History

- Symptoms
  - Fever
  - Chills
  - Night Sweats
  - Weight Loss
  - Cough
  - Productive Cough
  - Hemoptysis

- PMH:
  - Diabetes
  - HIV
  - Other Immunosuppression
  - Silicosis
  - Drug/alcohol/tobacco
  - TB exposures or Risk?
Clinical Evaluation: CXR

- Findings associated with higher risk of TB
  (require further evaluation and possible treatment for TB)
  - Noncalcified nodular lesions
  - Fibrotic scars

- Findings consistent with TB disease
  (require further evaluation and possible treatment for TB)
  - Enlarged hilar, mediastinal or subcarinal lymph nodes
  - Atelectasis
  - Alveolar consolidation
  - Interstitial infiltrates, cavitary and non-cavitary
  - Pleural effusion
  - Focal mass
  - Hyperinflation in children

- If CXR is abnormal, do not just treat for LTBI!
- You must rule out Active TB!

Atypical Presentation of TB

- HIV infection, chronic renal disease, diabetes, immunosuppression may alter presentation
  - CXR may be atypical; lower lobe infiltrate, adenopathy or completely normal
  - Negative TST or QTF Gold
  - Negative smear in up to 50%
  - Atypical clinical presentation
TB and AIDS: Radiographic Appearance

• The radiographic manifestations of HIV-associated pulmonary TB are dependent on the level of immuno-suppression.
  – Relatively intact cellular immune function (CD4 > 200): radiographic findings similar to non-HIV infected individuals (upper lobe, cavitary disease)
  – Severe immunosuppression (CD4 < 200): findings c/w primary disease or normal chest radiographs or dissemination with miliary pattern or extrapulmonary disease

PRIMARY TUBERCULOSIS
REACTIVATION TB

21st Century Algorithm

- Process Specimen
  - AFB Smear Microscopy
    - Inoculate Media
      - Species Identification
        - Drug Susceptibilities
          - Molecular DST

- Amplification-based Tests
  - 24 hours
  - 2 - 6 weeks
  - 2 - 3 weeks

16
Specimen Quality

- Accurate laboratory results are directly related to the quality of the specimen

- GOOD sputum  
  - Recently discharged material from the bronchial tree, with minimal amounts of upper respiratory tract secretions
    - Well coached patient, collect at least 3ml
    - Label tube and form - indicate test:
      - initial Dx: NAAT
      - isolation release: smear only
      - drug resistance suspected?

- Transport to lab cool and quickly
Acid Fast Microscopy (AFB Smear)

- Rapid & universally available
  - Used to support diagnosis and identify need to isolate
  - Detects the most infectious cases
  - Helps monitor response to therapy
  - Identify priority cases for nucleic acid amplification (NAA)
- Not sensitive
  - misses ~50% of TB
- Not specific in low TB prevalence areas (e.g. Texas)
  - Positive smear may be NTM
- Highly specific where TB is highly prevalent

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### AFB Smear

<table>
<thead>
<tr>
<th>CAP</th>
<th>ATS</th>
<th>Interpretation</th>
<th>AFB/ml sputum</th>
<th>Infectiousness of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>&lt;5,000</td>
<td>probably not infectious</td>
</tr>
<tr>
<td>1 or 2 per smear</td>
<td>1 or 2 per smear</td>
<td>weakly positive</td>
<td>~5,000</td>
<td>probably infectious</td>
</tr>
<tr>
<td>&lt;1 per field</td>
<td>1+</td>
<td>moderately positive</td>
<td>~10,000</td>
<td>probably infectious</td>
</tr>
<tr>
<td>1-10 per field</td>
<td>2+</td>
<td>moderately positive</td>
<td>~100,000</td>
<td>probably infectious</td>
</tr>
<tr>
<td>&gt;10 per field</td>
<td>3+</td>
<td>strongly positive</td>
<td>&gt;1,000,000</td>
<td>probably very infectious</td>
</tr>
<tr>
<td></td>
<td>4+</td>
<td>strongly positive</td>
<td>&gt;1,000,000</td>
<td>probably very infectious</td>
</tr>
</tbody>
</table>
Nucleic Acid Amplification Tests (NAAT)

• Tiny amounts of DNA/RNA are amplified (copied) until there is enough for easy detection

• DNA/RNA is examined
  • Identification
  • Detection of Drug Resistance

• Test turnaround time measured in hours

Nucleic Acid Amplification Tests (NAAT)

• Detects *M. tuberculosis* complex nucleic acids; does not distinguish between live and dead bacilli
  • For initial Dx specimens only
  • Not suitable for follow-up specimen or monitoring

• Sensitivity
  • >95% for AFB smear-positive TB patients
  • 55-75% of AFB smear-negative, culture-positive TB

• Does not replace culture
CDC Recommendations for NAAT
MMWR, 2009, 58:7-10

- “NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities”

- NAAT now recommended as standard practice!

Why Use A NAAT?

- Confirms AFB + case as M TB

- If AFB + case is NAAT negative on 2 specimens
  - **Suspect this is not M TB**
    - Suspend Contact investigation and
    - Hold TB treatment unless TB strongly suspected.

- If patient is not strongly suspected as M TB and is NAAT negative x 2,
  - **Remove from isolation.**
Who Should be Tested?

- CDC recommends NAAT on 1st sputum of every TB SUSPECT for whom the test result would alter case management or TB control activities
  - NAAT should NOT be ordered routinely if:
    - Hospital/commercial lab already has NAAT+
    - Clin. Susp. is extremely high, e.g. pt. symptomatic, smear+, Dx=TB, on Rx
      - i.e. when NAAT+ or – result would not change actions
    - Clin. Susp. very low, e.g. other Dx probable, spec is to r/o TB

- Definition of a “TB suspect” case can vary among providers

- TB programs, clinicians, and laboratorians must collaborate to develop criteria/definitions & policy for patients to be tested

How Do I Get a NAAT from the State Lab?

DSHS automatically performs NAAT on smear positive respiratory specimens, effective 3/1/2013
Cepheid GX MTB/Rif

• Practical NAAT
  – 15 minute entry-level technician versus 3-4 hrs using
    a highly skilled technician
• Highly accurate for smear positive TB
• Sensitivity uncertain for smear negative TB
• Limited data
  – Rifampin-R
  – Extra-pulmonary (CSF, gastric..)

AFB Culture

• Broth based system
  – MGIT, Trek, MB/BacT
• Solid medium
  – Purity
  – Middlebrook agar & LJ
**AFB Culture**

- More sensitive than smear
  - 5,000 to 10,000 AFB/ml for smear
  - 10 to 100 AFB/ml for culture
- Required for drug susceptibilities & genotype
- Requires a quality specimen
- Positive for only ~85-90% of PTB
  - May be negative due to contamination
- Lengthy
  - 1-6 weeks by liquid media
  - 2-8 weeks by solid media

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**Rapid Culture Identification**

- DNA probes
  - GenProbe
- HPLC (High performance liquid chromatography)
- Amplification-based tests
  - Lab Developed Tests (“home brew”)
    - Real time PCR
    - Molecular Beacons
  - DNA Sequencing
  - Line Probes
How Do NAAT and Culture Compare?

<table>
<thead>
<tr>
<th></th>
<th>NAAT</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial diagnosis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Detect Non-viable Mtb</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Suitable to Monitor Treatment</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Detect Drug Resistance</td>
<td>Some</td>
<td>Yes</td>
</tr>
<tr>
<td>Detect Drug Susceptible</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Genotype for Epidemiology</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Current NAATs are not sensitive enough to rule-out TB and they cannot replace culture.

*M. tuberculosis complex*

- All positive by NAAT & AccuProbe

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of Texas strains 2005-2010*</th>
</tr>
</thead>
<tbody>
<tr>
<td>– <em>M. tuberculosis</em></td>
<td>8,058 (98.6%)</td>
</tr>
<tr>
<td>– <em>M. bovis</em></td>
<td>79 (1.0%)</td>
</tr>
<tr>
<td>– <em>M. bovis BCG</em></td>
<td>15 (0.2%)</td>
</tr>
<tr>
<td>– <em>M. africanum</em></td>
<td>17 (0.2%)</td>
</tr>
<tr>
<td>– <em>M. caprae</em></td>
<td></td>
</tr>
<tr>
<td>– <em>M. microti</em></td>
<td></td>
</tr>
<tr>
<td>– <em>M. canettii</em></td>
<td></td>
</tr>
<tr>
<td>– <em>M. pinnipedii</em></td>
<td></td>
</tr>
</tbody>
</table>

* Data: Texas DSHS Laboratory Genotype Database
## Drug Susceptibility Testing (DST) of *Mycobacterium tuberculosis* Complex

### Current Recommendations

- Initial isolate should be tested against primary or first-line drugs (FLD)
  - INH, RMP, EMB, PZA
- For isolates resistant to RMP or to any 2 FLDs, test all second-line drugs
  - To include FQ, AMK/KAN, CAP, ETH, PAS
  - Not cycloserine; unreproducible

### Turnaround Time for MTBC Drug Susceptibility Testing (DST)

- Specimen receipt to 1<sup>st</sup> line DST by rapid broth: 4 to 5 weeks
- 2<sup>nd</sup> line drugs by rapid broth or agar proportion: additional 2 to 4 weeks
- Referral to reference lab adds more time

- Molecular methods can detect resistance to 1<sup>st</sup> & 2<sup>nd</sup> line drugs within 1 to 2 days
Detection of Genetic Mutations Causing Resistance

- Examining DNA of specific genes for mutations known to be associated with conventional phenotypic resistance

- Rapid - analysis takes less 1 day

- Can be done on isolates or directly on NAA+ specimens!

MTBC Molecular Drug Resistance Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>% of Resist.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>rpoB</td>
<td>97%</td>
</tr>
<tr>
<td>INH</td>
<td>katG &amp; inhA</td>
<td>86%</td>
</tr>
<tr>
<td>EMB</td>
<td>embB</td>
<td>79%</td>
</tr>
<tr>
<td>PZA</td>
<td>pncA</td>
<td>86%</td>
</tr>
<tr>
<td>F-quinolones</td>
<td>gyrA</td>
<td>80%</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>rrs</td>
<td>~75%</td>
</tr>
</tbody>
</table>
### CDC Molecular Detection of Drug Resistance (MDDR)

- Implemented Sept 2009 for isolates
- Expanded June 2012 for NAA+ specimens
- Test Indications
  - Known/suspect DR case or contact to DR case
  - Previous TB Treatment
  - Patient from area with high rate of DR TB
  - Mixed or nonviable culture

### CDC Molecular Detection of Drug Resistance (MDDR)

- Provides 48-72 hr DNA sequence analysis for drug resistance prediction
- MDDR supplements, not replaces, conventional DST
  - Used alone, MDDR and conventional DST are imperfect
  - Used together, accuracy of the detection of drug resistance can be improved.
- Conventional DST results are still essential to confirm susceptibility to individual drugs.
Inoculate Media

Species Identification

Drug Susceptibilities

21st Century Algorithm

Process Specimen

AFB Smear Microscopy

Molecular DST

Amplification-based Tests

Specimen received in the lab

At 24 hours, expect smear results

At 24 hours, expect results of NAAT or Molecular DST

At 48 hours, expect results of NAAT or Molecular DST

At 21 days, expect a culture ID (TB or NTM)

At 21 days, expect a culture ID (TB or NTM)

At 21 days, expect the culture to be finalized if negative

At 6-8 weeks, expect the culture to be finalized if negative

At 72 hours, expect results of IGRA

At 28 days, expect 1st line susceptibility results, expect 2nd line 4 weeks after requested

When should I consider my specimen delayed?

Day 0 1 2 3 21 28 42-56

At 24 hours, expect smear results

At 48 hours, expect results of NAAT or Molecular DST

At 21 days, expect a culture ID (TB or NTM)

At 6-8 weeks, expect the culture to be finalized if negative

At 28 days, expect 1st line susceptibility results, expect 2nd line 4 weeks after requested
Treatment of Tuberculosis

American Thoracic Society, CDC, and Infectious Diseases Society of America

USPHS/IDSA
Evidence-Based Rating Scale

• Strength of Recommendation
  – A = preferred
  – B = acceptable alternative
  – C = offer when unable to give A or B
  – D = should generally NOT be offered
  – E = should NEVER be offered

• Quality of Supporting Evidence
  – I – randomized clinical trial
  – II – clinical trial, not randomized
  – III – expert opinion
Short course treatment of drug susceptible TB

• Intensive phase
  – 4 drugs INH, rifampin, PZA, ethambutol
  – 8 weeks
    • Daily
    • Daily then BIW / TIW
    • TIW
• Continuation phase
  – 2 drugs INH, rifampin
  – 18 or 31 weeks
    • Daily
    • TIW
    • BIW

Duration of treatment

• 6 months
  – Requires INH, rifampin throughout and PZA during the initiation phase
• 9 months
  – If PZA was not used
  – Silico-TB
  – Prolongation to decrease risk of relapse
Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-I** *(HIV Uninfected)*

**Initial Phase**
2 mo H,R,Z,E daily (56 doses, 8wks) or
2 mo H,R,Z,E 5x/wk (40 doses, 8wks) then

**Continuation Phase**
-4 mo - H,R daily (126 doses, 18 wks) or
-4 mo – H,R 5x/wk (90 doses, 18 wks) or
-4 mo – H,R, 2x/wk (36 doses, 18 wks)

Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-II** *(HIV Uninfected)*

**Initial Phase**
2 weeks H,R,Z,E daily (14 doses) then
6 Weeks H,R,Z,E twice weekly (12 doses) then

**Continuation Phase**
4 months  H, R twice weekly (36 doses, 18 weeks)

Intermittent dosing by DOT only!
Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-III** (HIV Uninfected)

**Initial Phase**
2 weeks H,R,Z,E 5x per week (10 doses) *then*
6 Weeks H,R,Z,E twice weekly (12 doses) *then*

**Continuation Phase**
4 months H, R twice weekly (36 doses, 18 weeks)

Intermittent dosing by DOT only!

---

Treatment of Culture Positive Pulmonary TB

– THrice WEEKLY – “HONG KONG” REGIMEN

» Regimen Rated **BI** (HIV uninfected)

**Initial Phase**
• 2mo – H,R,Z,E 3x/week (24 doses, 8weeks)

**Continuation phase**
• 4mo – H,R 3x/wk (54 doses, 18 weeks)

Intermittent dosing by DOT only!
Newer drugs for treatment of TB

• Newer rifamycins
  – Rifabutin
    • HIV – TB
    • Unable to tolerate rifampin due to side effects
  – Rifapentine – long half life
• Fluoroquinolones: levofloxacin, moxifloxacin
  – Resistance to first line agents
  – Intolerance to first line drugs

Strategies to promote good outcome

• Patient centered care
• DOT provided by health department
• Monthly clinical evaluation in outpatient setting
  – Early detection of side effects
  – Educate and promote adherence to therapy
  – Address comorbidities that impact treatment response
• Monthly sputum until 2 consecutive negative cultures
Strategies to promote good outcome

• Assess patient related risk factors for poor outcome
  — Severity of disease
    • High bacillary burden
  — Co-morbid conditions
    • Liver disease
    • HIV
    • Poorly controlled DM
    • Malignancy
  — Adherence to therapy

Useful strategies

• Prolongation of treatment in delayed responders
• Increase frequency of dosing
• Evaluation and management of delayed response
• Serum drug level monitoring
Populations of Mycobacteria

- Actively dividing bacterial subpopulation
  - INH
    - Most potent drug for killing actively dividing bacteria
    - Associated with decrease in infectiousness

Importance of the Intensive Phase
Importance of the Intensive Phase

• Persisters
  – Revert back and forth to other subpopulations
  – Source of relapses
  – Rifampin is the only first line drug with activity against persisters

• Optimizing bactericidal and sterilizing activity early will minimize overall bacterial load present during continuation phase

2 month culture conversion

• Surrogate marker of sterilizing activity of drug regimen
• Used to predict likelihood of relapse
• Commonly considered to be 80% in 4 drug regimens
• More recent TBTC studies show lower rates
  – 71% Moxifloxacin vs Ethambutol*
  – 60% Moxifloxacin vs INH**

*Study 27 AJRCCM 2006
** Study 28 AJRCCM 2009
### Adverse outcomes

- **Delayed response**  
  – Culture conversion after 3 months effective regimen
- **Treatment failure**  
  – Persistent + culture after 4 months treatment
- **Relapse**  
  – Symptoms or culture positive after completion of treatment
- **Development of drug resistance**

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### Delayed Response

#### Culture Positive at 3 Months

- TB lab should **automatically repeat** susceptibility studies on last positive culture - check to be sure
- Assess adherence
- Consider serum drug levels
- Evaluate response to therapy  
  – Clinically and radiographically

> **By the time you know this it is 4 months into therapy!**
Treatment Failure
Culture Positive at 4 Months

Clinical evaluation
Repeat susceptibility studies
  • On last positive culture
  • And request on a “new sputum culture” now
    – Ask for molecular detection of drug resistance
Serum drug levels if not previously done
Augment therapy
  • Add at least two and preferably three new drugs to which the isolate is likely to be susceptible
  • Even if no clinical or radiographic evidence of failure

MMWR Treatment of Tuberculosis 2003; 52

Relapse

• Circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis drugs but at some point after completion of therapy, either becomes culture-positive again or experiences clinical and radiographic deterioration consistent with active tuberculosis

• Try to identify “WHY” your patient relapsed so you can do it right this time!
TBTC STUDY 22: RATE OF FAILURE or RELAPSE, BY REGIMEN, SPUTUM CULTURE, AND CHEST RADIOGRAPH

![Graph showing rate of failure or relapse by culture result and chest radiograph.]

Lancet 2002; 360:528

End of Therapy (EOT) Cavity: A Risk Factor for Relapse

![Graph showing proportion of subjects with tuberculosis relapse by findings on early and EOT CXR. EOT = end of treatment; CXR = chest radiograph.]

Hamilton; Int J Tuberc Lung Dis 2008
Lack of Weight Gain and Relapse Risk, TBTC Study 22

- Relapse risk high in those underweight at diagnosis 19.1% versus 4.8%

- Among pts underweight at diagnosis, if weight gain ≤ 5% after 2 months of treatment:
  - Relapse risk 18.4% vs. 10.3%
  - If also cavitary disease: 18.9%
  - If cavitary and + 2 month culture: 50.5%


Risk factors for relapse

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Rate</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary and culture positive 8 weeks</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Cavitary</td>
<td>4.7%</td>
<td>4.7</td>
</tr>
<tr>
<td>Culture positive 8 weeks</td>
<td>5.9%</td>
<td>5</td>
</tr>
<tr>
<td>Non Hispanic White race</td>
<td>13.5</td>
<td>2.4</td>
</tr>
<tr>
<td>* &gt;10% ideal body weight and failure to gain weight &gt; 5% at 8 weeks</td>
<td>18.4%</td>
<td>3.8</td>
</tr>
<tr>
<td>^ Beijing strain in Asia Pacific Islander</td>
<td>OR:11</td>
<td></td>
</tr>
</tbody>
</table>

Lancet 2002; 360:528
*AJRCCM 2006; 174:344
^Emerging Infect Dis 2009; 15:1061
### Treatment Related Risk Factors for Early Relapse of TB

- Evaluation of 113 cases of relapsed TB, matched with case controls
  - Non-cavitary TB, thrice weekly, 6 mo relapse rate: 1.1%
  - Cavitary TB relapse rates:
    - Thrice weekly, 6 mo: 7.8%
    - Daily, 6 mo: 3.3%
    - Extended thrice weekly: 0.5%
    - Extended daily: 0.4%
      - Either intensive phase or CP was beneficial

Am J Respir Crit Care Med. 2004; 170: 1124-30

### Treatment Related Risk Factors for Early Relapse - Dosing Intensity

Risk of relapse of 6 month regimen and dosing schedule, controlling for initial cavitation and 2 month sputum culture

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily IP, thrice weekly CP</td>
<td>1.6 (0.6 – 4.1)</td>
</tr>
<tr>
<td>Daily IP, twice weekly CP</td>
<td>2.8 (1.3 - 6.1)</td>
</tr>
<tr>
<td>Thrice weekly IP, CP</td>
<td>2.8 (1.4 – 5.7)</td>
</tr>
<tr>
<td>Daily IP, weekly rifapentine</td>
<td>5.0 (3.3-15.3)</td>
</tr>
</tbody>
</table>

Am J Respir Crit Care Med 2006; 174: 1153
Treatment Related Risk Factors for Early Relapse-Dosing Intensity

• In cavitary disease (regardless of 2 month culture), risk of relapse of 6 month regimen > 5% except,
  – Daily IP, CP
  – Daily IP, thrice weekly CP

• In cavitary disease and 2 month culture +, risk of relapse is 6% in
  – Daily IP, CP
  – Daily IP, thrice weekly CP

Am J Respir Crit Care Med 2006; 174: 1153

Treatment of TB and Optimal Dosing Schedules

Kwok Chiu Chang, Chi Chiu Leung, Jacques Grosset, Wing Wai Yew

Thorax 2011 66:997-1007

Systematic Review of 32 articles – 9 systematic reviews, 8 controlled studies, 9 PK-PD studies, and 6 animal studies.

Levels of evidence and grades of recommendations assigned according to clinical evidence with reference to Scottish Intercollegiate Guidelines
Non HIV related TB (11 studies)

• Suggests that intermittent dosing reduces TB treatment efficacy shown by a higher risk of relapse or failure

• Negative impact most prominent in presence of cavities

• Standard 6 mo regimen - no significant difference between daily throughout and daily in initial phase

Level of evidence: 1+
Grade of recommendation: “A”
• Avoid intermittent doses, especially in initial phase and in presence of cavities

TB With INH Resistance (2 studies)

• Suggests that dosing intermittency reduces TB treatment efficacy as shown by:
  – Higher risk of treatment failure, relapse or acquired drug resistance

Level of evidence 1+
Grade of evidence: “A”
– Avoid dosing intermittency, especially in the initial phase in the presence of INH resistance
HIV related TB (3 studies)

- Suggests intermittent Rx, especially in initial phase reduces treatment efficacy as shown by
  - a higher risk of treatment failure, relapse, or acquired Rifampin resistance

Level of evidence 1+
Grade of recommendation “A”
- Avoid intermittency, especially in the initial phase in HIV TB

Prolongation of Continuation Phase

Continuation phase increased to 7 mo if initial CXR is cavitary & culture is positive at 2 mo
Treatment of Tuberculosis MMWR 2003

- Rational for Extending Therapy
  - Continuation of PZA for an additional 2 months was not helpful in drug susceptible disease
  - Prolongation of continuation phase by 2 months decreased relapses in silico-tuberculosis from 20% to 2%
Effect of Prolonging Therapy on Treatment Failure or Relapse

**Treatment of Silico-tuberculosis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SHRZ - 6mo* (n=49)</th>
<th>SHRZ – 8mo* (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>20%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Three times weekly therapy  
Am Rev Respir Dis 1991;143:262-267

Factors Associated with Relapse of Tuberculosis

<table>
<thead>
<tr>
<th>Disease related</th>
<th>Treatment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cavitation</td>
<td>• DOT</td>
</tr>
<tr>
<td>• Bilateral disease</td>
<td>• Adherence</td>
</tr>
<tr>
<td>• Sputum culture at 2 months</td>
<td>• Dosing intensity</td>
</tr>
<tr>
<td>• Low body weight</td>
<td>• Duration of therapy</td>
</tr>
<tr>
<td>• Lack of weight gain</td>
<td>• Use of rifamycin</td>
</tr>
<tr>
<td>• Drug resistance</td>
<td></td>
</tr>
<tr>
<td>• ?Beijing strain in Pacific Islander</td>
<td></td>
</tr>
<tr>
<td>• Other comorbidities</td>
<td></td>
</tr>
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In the Treatment of TB, You Get What You Pay For...

• “A consistent theme has begun to appear: more extensive disease requires more treatment, and the fewer total doses, the higher the risk that treatment will prove inadequate”

  – What should we conclude?
    • First: More treatment means more cures
    • Second: Programs need to consider some individualization of therapy
    • Third: Should not deter us from intermittent therapy but should remind us of need for sophisticated management based on case-specific circumstances
      – Should not be surprised that individuals differ in their response.


Tailoring Treatment Regimens

• **Prolong** continuation phase when:
  – Positive 2 month culture with cavitary disease
  
  – Extrapulmonary disease
    • Meningitis
    • Disseminated disease in children
  
  – HIV TB in children and adolescents

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Tailoring Treatment Regimens

• **Consider** - Prolongation of continuation phase:
  
  – Slow clinical or radiological response
  
  – Positive 2 month culture **OR** cavitary disease?
  
  – End of therapy (EOT) cavity present
  
  – >10% below ideal body weight?

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Tailoring Treatment Regimens

• Daily IP
  
  – cavitary disease
  
  – HIV TB
  
  – INH resistance
Relapsed Tuberculosis Management Strategies

• Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later

• Microbiological Confirmation of Relapse Should be Pursued Vigorously
  – Confirm relapse bacteriologically
  – Identify drug susceptibility pattern of isolate
  – Use DNA fingerprinting to identify new infection causing the disease versus relapse

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Relapsed Tuberculosis Management Strategies

• Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms

  Treat with standard RIPE regimen

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Relapsed Tuberculosis Management Strategies

• If culture & susceptibility studies (those treated in other countries) were not done but treatment given by DOT
  – Usual treatment with RIPE
    • Watch carefully for clinical deterioration
  – Consider an expanded regimen if immune suppressed, significantly ill, or extensive disease
    • Use at least 2 drugs to expand the regimen
    • (Molecular testing for drug resistance)

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Relapsed Tuberculosis Management Strategies

• Suspect drug resistance if:
  – Patients treated with self administered therapy
  – Patient was poorly adherent
  – Patient deteriorates clinically or radiographically during initial weeks of treatment

• Do molecular testing for drug resistance
  • Consider expanded regimen, especially if immune suppressed
  • Add at least 2 (fluoroquinolone and an injectable)
Treatment in Special Situations

Active TB During Pregnancy

- Diagnosis may be difficult
  - Respiratory symptoms common in late pregnancy
  - Reluctance to do a CXR
  - Extra-pulmonary disease is even more difficult

- Outcomes for BOTH mom and baby are improved with treatment during pregnancy

- Infection control is important at time of delivery if mom is still infectious
Active TB During Pregnancy

• Treatment:
  – INH, Rifampin, Ethambutol x 9 months
    • Stop ethambutol if susceptible to INH and rifampin
  – PZA only if drug resistance is present
    • PZA regarded as safe by most countries in world

• Follow carefully for hepatotoxicity- risk is increased
  – During pregnancy
  – Three months postpartum
TB and DM

• 65 male, HbA1C, former smoker
  – Large soft tissue abscess R thigh
  – Abnormal CXR – RUL thick walled cavity
  – Sputum smear negative x3
  – Bronch: chronic inflammation and +AFB
  – Pansensitive
  – Standard therapy one week later and discharged

TB and DM

• Slow clinical improvement and cultures remained positive
• Switched to INH-rifampin after 8 weeks IP
• On 5th month – sputum turned smear + and later reported INH R
• Rifampin, Ethambutol, PZA, fluoroquinolone and streptomycin
• Side effects from strep and capreomycin with nausea, cramps and aches
TB and DM

- Endocrine attending started on insulin therapy
- Strep and capreomycin stopped due to adverse effects
- PZA stopped due to uric acid 9
- DST: only INH resistance
- Rifampin, FQ, ethambutol continued to 9 months after INH R developed
- Continued to complain of muscle pain in the limb girdles
Tuberculosis Drug Serum Level Monitoring Recommended

• Delayed response to therapy
• Advanced AIDS with evidence of malabsorption
• Seriously ill patient to maximize therapy
• ? Diabetics
• Toxicity evaluation
• Use of second line drugs
• Acquired drug resistance
• Relapse
• Potential for drug-drug interactions
• Renal and hepatic insufficiency

Management of TST + Persons With an Abnormal CXR and – AFB Smear

<table>
<thead>
<tr>
<th>Isolated CXR with nodules and/or fibrotic lesions:</th>
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<tbody>
<tr>
<td>• If no symptoms - wait</td>
</tr>
<tr>
<td>– Collect sputum culture</td>
</tr>
<tr>
<td>– Evaluate for symptoms</td>
</tr>
<tr>
<td>– Repeat CXR</td>
</tr>
<tr>
<td>• If CXR stable at 2 – 3 months and cultures are negative, treat as LTBI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isolated CXR with nodules and/or fibrotic lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If patient has any signs or symptoms of TB disease:</td>
</tr>
<tr>
<td>patient is a TB suspect</td>
</tr>
<tr>
<td>• Start 4 drugs</td>
</tr>
<tr>
<td>• Never start a single drug in a patient with possible active TB</td>
</tr>
</tbody>
</table>
Culture Negative TB

- TB suspect with positive TST or IGRA
  - Risk factors for TB
  - Abnormal CXR
  - Usually – clinical symptoms

- All cultures are negative

- Classify based on clinical and/or radiograph response to treatment at 2 months
  - Clinical or CXR improvement – Culture Negative TB
  - Treat for 4 months (children and HIV + 6 months)
  - RIPE for 2 months, then RIE +/- PZA dependent on INH resistance

Management of Treatment Interruptions

- Initial phase of therapy
  - <14 days – complete standard # of doses
  - >14 days – restart from the beginning

- Continuation phase
  - ≥80% doses by DOT – if initial smear−, may stop
  - < 80% doses by DOT and/or initial smear +
    - Repeat culture
      - Management based on clinical and bacteriological factors.

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Where to Get More Information

- HEARTLAND NATIONAL TB CENTER
  - 1-800-TEX LUNG: Medical Consultation and Technical Assistance Line
  - Future training courses
- CDC
- TB Educate
- TBresources.com